Erythropoiesis Stimulating Agents Criteria for Use for Hepatitis C Treatment-Related Anemia

Criteria for Use

March 2013

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives,
Office of Public Health and Hepatitis C Resource Centers

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.** *The Product Information should be consulted for detailed prescribing information.*

Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT receive recombinant erythropoietin*

☐ Uncontrolled hypertension
☐ Risk for thrombosis
☐ Known hypersensitivity to mammalian cell-derived products or known hypersensitivity to albumin

Inclusion Criteria . *All must be selected for patient to be eligible*

☐ Patient receiving hepatitis C therapy (peginterferon, ribavirin, with or without boceprevir or telaprevir)

☐ Patient underwent evaluation for other causes of anemia (e.g. bleeding, nutritional deficiency) and has been treated appropriately (Refer to Issues for Consideration)

☐ Patient develops anemia defined as Hgb <10 g/dL (or as clinically indicated for significant anemia-related signs and symptoms) and persists for at least 2 weeks after reducing the ribavirin dose to 600mg/day (either through 200mg incremental dose reductions or one-time dose reduction to 600 mg/day)

Exception: the use of an erythropoiesis stimulating agent (ESA) may be considered prior to ribavirin dose reduction in patients receiving peginterferon/ribavirin alone with documented evidence post-liver transplantation or HIV/HCV co-infection

☐ Provider has discussed with patient the potential risks and benefit of ESA therapy and a shared decision has been made for use (Refer to Issues for Consideration)

Dosage and Administration

ESA are only FDA approved for use in patients with chronic kidney disease and cancer patients with anemia from myelosuppressive chemotherapy; therefore, prescribing information recommendations are specific to these patient populations.

Consider initiating: epoetin alfa 40,000 units subcutaneously once weekly OR darbepoetin alfa 200 mcg subcutaneously every other week.

Recommended Monitoring for Response

Goals of ESA therapy for hepatitis C related anemia include resolution of anemia with target to not exceed Hgb of 11g/dL while maintaining ribavirin dose of ≥600mg/day, and reducing need for blood transfusion and/or hospitalization. Providers and patients should weigh the possible benefits of decreasing transfusions against the increased risks of death and other serious cardiovascular adverse events.

- Response should be assessed at least every 2 weeks until Hgb is stable.
- Providers should use the lowest dose of ESA sufficient to reduce the need for RBC transfusions to alleviate symptoms.
- If the hemoglobin level rises to exceed 10 g/dL, reduce or interrupt the dose of ESA to prevent the hemoglobin from rising to >11 g/dL.
- The optimal Hgb level in patients with hepatitis C is unknown. **Therapy needs to be individualized on a case by case basis.** For patients who tolerate Hgb <10 g/dL, the initiation of ESA can be deferred or a ESA treatment target of <10 g/dL may be appropriate.
- If the hemoglobin rises rapidly (e.g., more than 1 g/dL in any 2-week period), reduce the dose of epoetin alfa or darbepoetin by 25% or 40%, respectively, or more as needed to reduce rapid responses.

Issues for Consideration

Ribavirin Dose Reduction

- Initial management of HCV treatment-related anemia should consist of ribavirin dose reduction for hemoglobin <10g/dL (or as clinically indicated for significant anemia-related signs and symptoms).

Role of ESAs in boceprevir- or telaprevir-containing regimens

- In both boceprevir- and telaprevir-containing clinical trials, management of anemia in the clinical trial protocols involved ribavirin dose reductions in accordance with the ribavirin product labeling. In these clinical trials, ribavirin dose reduction to

600mg did not appear to compromise SVR. Of note, the use of ESAs was generally prohibited in the telaprevir Phase 3 trials while the boceprevir trials allowed use of epoetin alfa according to investigator's discretion. Only 1% of patients in the telaprevir trials received an ESA. No clinical trial data are available with use of darbepoetin alfa.

- The addition of boceprevir or telaprevir in combination with peginterferon alfa/ribavirin has been associated with an increased incidence of anemia. In clinical trials, the average additional decrease of hemoglobin was approximately 1-1.5 g/dL in boceprevir- and telaprevir-treated patients following recommended strategies for anemia management. Hgb levels may increase after boceprevir or telaprevir is discontinued; note that telaprevir is administered only for the first 12 weeks in combination with peginterferon alfa/ribavirin while boceprevir may be administered between 24 and 44 weeks in combination with peginterferon/ribavirin.
- **If ribavirin is discontinued or interrupted for equal or greater than 7 days in patients who are concomitantly receiving an HCV Protease Inhibitor (i.e. boceprevir or telaprevir), the HCV Protease Inhibitor must also be discontinued.**
- In February 2013, the prescribing information for boceprevir was updated to include results from a randomized, parallel-arm, open-label clinical trial that compared the use of an ESA versus ribavirin dose reduction for initial management of anemia during therapy with boceprevir in treatment-naïve HCV patients with genotype 1. Similar SVR rates were reported in subjects who were randomized to receive ribavirin dose reduction compared to subjects who were randomized to receive an ESA. **In this trial, use of ESAs was associated with an increased risk of thromboembolic events including pulmonary embolism, acute myocardial infarction, cerebrovascular accident, and deep vein thrombosis compared to ribavirin dose reduction alone.** The treatment discontinuation rate due to anemia was similar in subjects randomized to receive ribavirin dose reduction compared to subjects randomized to receive ESA (2% in each group). The transfusion rate was 4% in subjects randomized to receive ribavirin dose reduction and 2% in subjects randomized to receive ESA. The prescribing information states that ribavirin dose reduction is recommended for the initial management of anemia.

Role of ESAs in pegylated interferon and ribavirin <u>only</u> containing regimens

- Published data from several clinical trials have shown that ribavirin dose reduction to 600mg in the setting of anemia (Hgb </= 10g/dL) was not associated with lower SVR rates or higher relapse rates in patients receiving therapy with peginterferon alfa/ribavirin dual therapy (Reddy et al Clin Gastro and Hepatol 2007; 5:124–129, Shiffman et al Clin Gastro and Hepatol 2007;132:130-112, Sulkowski et al Gastoeterology 2010;139: 1602-1610).

Evaluation for other causes of anemia (e.g. bleeding, nutritional deficiency):

- Obtain CBC and the following as indicated: peripheral smear, reticulocyte count, B12, folate.
- Assess for adequate iron stores. If evidence of iron deficiency is found (ferritin <100 ng/mL or transferrin saturation <20%), replete iron prior to therapy and investigate causes of iron deficiency.
- Obtain thyroid function tests as thyroid dysfunction may impact response to erythropoietin. Assess for thyroid abnormalities and treat appropriately.

Safety

- Use the lowest ESA dose sufficient to reduce the need for red blood cell (RBC) transfusions; providers and patients should weigh the possible benefits of decreasing transfusions against the increased risks of death and other serious cardiovascular adverse events.
- In controlled trials of patients with chronic kidney disease, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered ESAs to target a hemoglobin level of greater than 11 g/dL. **The prescribing information states that no trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks**.
- In the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial, over 1400 patients not on dialysis were randomized to epoetin alfa with two different target Hgb levels. The study found that patients in the higher Hgb target group (13 – 13.5 g/dl) had a shorter time to the primary endpoint (the composite outcome of death, myocardial infarction, hospitalization for congestive heart failure, or stroke) compared to patients in the lower Hgb target group (10.5 – 11 g/dl) (hazard ratio of 1.3; 95% CI 1.03, 1.74; p=0.03). The average Hgb at the end of the study was 12.6 g/dL for the high Hgb group and 11.3 g/dL for the low Hgb group. For further details, refer to National PBM Communication in 2007 http://www.pbm.va.gov/vamedsafe/National%20PBM%20Bulletin%20ESA%20Final.pdf
- In the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT), 4038 patients with CKD, diabetes, and anemia (Hgb < 11 g/dl) were randomized to treatment with darbepoetin alfa to a target Hgb of 13 g/dL (median 12.5 g/dL), or placebo with rescue darbepoetin alfa therapy for Hgb < 9 g/dL (median 10.6 g/dL). There was no significant difference in the primary endpoints of death or CV events and of death or end-stage renal disease between treatment groups; however, there was a significant increase in fatal or nonfatal stroke (HR 1.92;95% CI 1.38 to 2.68; P<0.001) in patients treated with an ESA in the higher Hgb target group. Based on the outcomes in TREAT, for every 100 subjects treated with darbepotein compared to control, ~5 additional subjects will avoid transfusion while ~1 additional subject will have a stroke. For subjects with prior history of stroke, ~5 additional subjects will avoid transfusion while ~3.5 additional subject will have another stroke (www.fda.gov; Trial to TREAT CRDAC Meeting). For further details, refer to National PBM Communication in 2011 http://www.pbm.va.gov/VACenterForMedicationSafety-Index.aspx
- In cancer patients, ESA shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of certain cancer types.
- In patients who had a rise in Hgb >1 g/dL during any 2-week period while on recombinant erythropoietin, there was an

increased incidence of cardiac arrest, neurologic events (including seizures and stroke), exacerbation of hypertension, congestive heart failure, thrombotic events, and fluid overload. Neurologic symptoms should be monitored closely. Blood pressure should be closely monitored and controlled while receiving an ESA.

- Cases of pure red cell aplasia (PRCA) and of severe anemia, with or without other cytopenias, associated with neutralizing antibodies to erythropoietin have been reported in patients treated with ESAs. Any patient who develops a sudden loss of response to ESAs accompanied by severe anemia and low reticulocyte count, should be evaluated for the etiology of loss of effect, including the presence of neutralizing antibodies to erythropoietin. If anti-erythropoietin antibody-associated anemia is suspected, withhold the ESAs. Assays for binding and neutralizing antibodies should be performed. ESAs should be permanently discontinued in patients with antibody-mediated anemia. Patients should not be switched to other ESAs as antibodies may cross-react.

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